

The Spectrum of Clinical Utilities in Molecular Pathology Testing Procedures for Inherited Conditions and Cancer: A Report of the Association for Molecular Pathology

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INTRODUCTION

The roles of clinical validity and clinical utility in determining the medical usefulness of a molecular pathology testing procedure have been the subject of debate for a number of years, and discussions have increased since the advent of new molecular pathology Current Procedural Terminology (CPT®) codes.ⁱ Establishment of clinical validity is fundamental to clinical utility (Table 1); qualitative criteria for clinical validity have historically been the standard for insurance coverage determinations¹. The rising cost of targeted therapies for patients whose molecular test results indicate a likelihood of response has payers reacting to potentially unsustainable payments and the ominous specter of concomitant premium increases. According to a recent study by the IMS Institute for Healthcare Informatics, the average monthly price of cancer therapy in the U.S. increased 39% in the ten year period 2004-2014, from \$14,821 to \$20,700, when adjusted for inflation; and, targeted therapies accounted for almost 50% of total spending on all oncology medicines (Developments in Cancer Treatments, Market Dynamics, Patient Access and Value: Global Oncology Trend Report 2015, <http://www.imshealth.com/>, last accessed 8/15/2015.. The variety of testing methodologies utilized to identify patients that might benefit from targeted therapies is becoming numerous and more complex. The increasing complexity of molecular diagnostic testing procedures, especially Gene Expression Signatures and Next Generation Sequencing (NGS) tests, is one of the factors payers cite for their interest in more comprehensive scrutiny. Title XVIII of the Social Security Act, Section 1862(a)(1)(A) prohibits Medicare payment " ...for items or services

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which are not reasonable and necessary for the diagnosis and treatment of illness or injury...." with certain exceptions. Recently, several Medicare Medical Administrative Contractors (MACs) have associated evaluations of both analytical and clinical validity with Medicare's reasonable and necessary requirement and have demanded evidence for both in addition to evidence of clinical utility (CMS Local Coverage Determination Palmetto L33599; CGS DL36021; Noridian L33541, www.cms.gov, accessed 8/11/2015). NGS gene panels and even NGS exome testing may be cost effective compared with testing several known relevant genes by Sanger sequencing. A potentially large but indirect cost of large gene panels, especially in cancer treatment, is that they increase the likelihood of finding a mutation for which there is an expensive therapy, possibly off-label, or in a clinical trial. This impacts discussion of costs in complex ways; but it is evident that providers find the mutation analysis to have clinical utility, as they are taking action based on the test results. Alternately, gene panels or exome testing for inherited disease may identify variants that aren't well characterized and may trigger a cascade of other medical procedures, which may or may not be necessary.

Practical challenges in demonstrating clinical utility for molecular pathology testing procedures exist under any model. The general principles for evaluating clinical utility in molecular diagnostics are the same as for any test in medicine, from imaging to clinical chemistry, but the clinical questions addressed by molecular diagnostics often have features that limit the type and availability of evidence to assess clinical utility. For inherited disorders, constraints include low prevalence for specific disorders (although high in aggregate), lack of targeted therapies for most diseases, difficulty quantifying the impact of testing on psychological well-being and long-term care, and difficulty obtaining pertinent information about a patient's relatives. For cancer therapy, limitations include a low frequency for many driver mutations in a given type of cancer, even lower frequency for combinations of driver mutations, prolonged cancer clinical trials due to low levels of patient recruitment, and the paucity of broad molecular profile data in most cancer trials to date. Despite the challenges, patient-centered clinical molecular diagnostics, including

interpretation, conducted by appropriately trained and certified molecular pathologists or clinical medical geneticists can demonstrate compelling clinical utility, as described in the following examples throughout this document. While the scope of this report is restricted to molecular pathology testing procedures for inherited conditions and cancer, we believe many recommendations can be extended to additional applications of molecular testing.

CLINICAL UTILITY HAS MANY FACES

Molecular diagnostic tests are used for multiple purposes, ranging from diagnosis of disease in patients, risk assessment of an inherited disease in family members, evaluation of patients whose family history indicates they are at high risk of a disease, prediction of future disease, prognosis, and therapy selection. Some tests can be used for multiple indications; thus, the clinical utility of molecular diagnostics is context dependent. The Medical Test Methods Guide presented by the Agency for Healthcare Research and Quality (AHRQ) in 2012 provides a foundation to evaluate all medical tests, including molecular diagnostic tests². The fundamental tenets include the assertion that the value of a medical test must always be linked to the context of use. While clinical utility has many aspects, the ultimate goal is to provide information necessary to care for the patient or a family member, who could be either future or as yet undiagnosed patients. Molecular testing can impact patients and their care in numerous ways and needs to be incorporated into the global patient assessment and management, especially in the context of patient-centered care (Supplemental Figures 4 and 5). The decision to perform molecular diagnostic testing is made by the treating clinician based on the patient's symptoms, history, and clinical findings, often after pre-test consultation with a molecular pathology/medical genetics professional. Patient management occurs in the context of a medical team, where molecular diagnosis is integrated with additional clinical findings. The reasons for testing are most commonly classified as diagnosis, prognosis, and prediction. Of these, diagnosis is the foundation.

DIAGNOSIS

Importance of Molecular Diagnosis in Inherited Diseases

Establishing a diagnosis by molecular genetic testing procedures for a patient with an inherited or *de novo* genetic germline disorder has inherent clinical utility even in the absence of guided therapy. Historically, inherited conditions were diagnosed based on clinical history and phenotype. This clinical paradigm – a treating physician forms an initial clinical impression, including a differential diagnosis and orders the appropriate clinical or confirmatory tests– is still applicable to molecular diagnostics.

For many inherited diseases, the phenotype does not point to a definitive diagnosis. Even classic Mendelian single gene disorders can present challenges such as variable expressivity, locus heterogeneity, allelic heterogeneity, and incomplete (or reduced) penetrance. Basing a diagnosis on phenotype alone can result in incorrect diagnosis or delayed time to diagnosis. Making the correct diagnosis in a timely manner can have significant impact on patient, family, and physician decision-making by clarifying level of risk and prognosis, treatment options, and associated comorbidities. The correct genetic diagnosis can provide recurrence risk for the family and thereby facilitate preconception intervention or prenatal diagnosis for at-risk relatives.

In patients with suspected genetic disorders, the standard of practice has been to follow phenotype-driven iterative algorithms, single-gene-test-at-a-time, including radiographic studies, biopsies, metabolite analysis, and cytogenomic analysis. Despite these efforts, the majority of patients remain without a diagnosis³. Consecutive negative results can delay a definitive diagnosis and allow development of adverse consequences (i.e. increased morbidity). Termed the diagnostic odyssey, this approach to diagnosis is expensive and causes frustration to the patient, their family, and the clinicians.

When inherited genetic disorders have substantial genotypic and/or phenotypic overlap, testing several candidate genes simultaneously by a multi-gene panel may be appropriate. Although this can and has been done with classical Sanger sequencing, a multi-gene panel analyzed by massively parallel

sequencing can result in a faster time to diagnosis and reduced cost. An example is the class of aortic dysfunction or dilation syndromes, which include Marfan syndrome, Loeys Dietz syndrome, Ehlers Danlos syndrome type IV, and arterial tortuosity syndrome (GeneReviews®, http://www.ncbi.nlm.nih.gov/books/NBK1335/#_marfan_Management, accessed 6/5/2015). Genomic sequencing panels for this overlapping group of genetic disorders include sequencing most causative genes (e.g. *FBN1*, *TGFBR1*, *TGFBR2*, *COL3A1*, *MYH11*, *ACTA2*, *SLC2A10*, *SMAD3*, and *MYLK*). Even though symptoms are overlapping, distinguish between these diseases is important because the clinical course of each syndrome differs.

The utilization of multi-gene panels has increased with the advent of massively parallel sequencing (MPS) technologies, notably with clinical introduction of whole exome sequencing (WES)⁴. For well-defined clinical phenotypes an MPS gene panel can show modestly superior performance relative to WES. For disorders such as developmental delay or neurological disorders that show extensive genotypic and/or phenotypic overlap, WES is appropriate. WES can also reveal incidental pathogenic variants not related to the patient's phenotype but that are associated with treatable genetic diseases, such as hereditary breast cancer syndromes or familial hypercholesterolemia⁵. Detection of such variants provides a preventative medicine opportunity for both the proband and at-risk family members.

Several thousand clinical exomes have been completed and many results summarized in the medical literature. These show the feasibility of establishing diagnoses for rare, clinically unrecognizable, or puzzling disorders that are suspected to be genetic in origin, and in many cases, delineating new genetic disorders^{6–11}. Currently the diagnostic yield for WES in this setting is approximately 25%⁴, but can be up to 50% depending upon clinical presentation and/or availability of family studies. This number is expected to rise as many more exomes are sequenced in national surveys (e.g. U.K. 100K study, U.S. Veteran's Administration Million Veteran Study, Clinical Sequencing Exploratory Research Consortium). A recent review of molecular diagnostic testing menus in US laboratories revealed that over 100 inherited

disorder-specific multi-gene testing panels are used clinically¹². Recognizing the increased clinical use of MPS, the American Medical Association has established genomic sequencing current procedural terminology (CPT) codes for several inherited genetic conditions, including gene panels such as aortic dysfunction, exomes, and genomes. Notably, the Blue Cross Blue Shield Association Technology Evaluation Center favorably assessed whole exome sequencing for suspected inherited disorders and defined clinical utility as the attainment of a diagnosis, not the direct effect on health status (Blue Cross and Blue Shield, http://www.bcbs.com/blueresources/tec/vols/28/28_03.pdf, accessed 6/5/15). At present whole genome sequencing (WGS) is considerably more expensive than WES, requires greater analysis, and generates more variants of uncertain significance. As technology advances, the balance of costs and reliability could tip in favor of WGS but at present WES is a plausible approach for inherited disease testing when the clinical picture does not strongly suggest a specific disorder suitable to a specific gene panel¹³.

Importance of Molecular Diagnosis in Oncology

The diagnosis of malignancy does not routinely rely on molecular diagnostics to the same degree as diagnosis of inherited disease; however, there are situations in which molecular diagnostic testing serves an important role in distinguishing benign from malignant proliferations. For example, molecular studies of the antigen receptor genes can help distinguish lymphoma from benign lymphoproliferations in cases which remain unclear after morphologic, immunohistochemical and flow cytometric analysis^{14,15}. Similarly, molecular mutation analyses in cystic neoplasia of the pancreas and of thyroid lesions of indeterminate cytology can be used to help differentiate benign from malignant lesions^{16–25}. In suspected myelodysplasia, National Comprehensive Cancer Network (NCCN) guidelines recommend testing a panel of genes to establish presence of “clonal hematopoiesis.” Molecular testing is often the testing modality of choice to provide a definitive diagnosis. Multiplex mutational analysis can establish a diagnosis especially when other traditional tests such as conventional cytogenetics, FISH testing, and flow

cytometric analyses are not definitive (NCCN Clinical Practice Guidelines in Oncology: Myelodysplastic Syndromes, Version 2, 2015, www.nccn.org/professionals/physician_gls/pdf/mds.pdf, accessed 5/6/2015).

Stratification of cancer has now become a part of the primary diagnosis. Accurate molecular diagnosis is fundamental to understanding the pathology of the disease process, which, in turn, will inform proper clinical management of the patient. The most extensive example is the World Health Organization (WHO) classification of lymphomas and leukemias which requires molecular diagnostic data for many of the tumor categories^{14,26}. In turn, correct molecularly-assisted diagnosis is essential to evidence-based management of patients²⁷. For example, until only a few years ago, the diagnosis of lung cancer included histologic classification only (e.g. non-small-cell lung carcinoma, adenocarcinoma). Now, mutation status has become a part of the disease name of an increasing number of cancers because they predict recurrence or have implications for targeted therapy, sometimes for multiple mutations (e.g., *BRAF*, *MEK*, RAS-mutant melanoma^{28–30}). MPS can interrogate multiple gene regions that have been characterized as mutational hot spots, providing an efficient method for identifying a number of somatic mutations known to be important cancer drivers^{17,31–33}. Just as important as diagnostic efficiency is the limitation presented by specimen type, which can impact the number of tumor cells and/or quantity of DNA available for analysis. Lung cancer patients benefit from the introduction of minimally invasive procedures such as bronchoscopy and mediastinoscopy that avoid surgical biopsy; however, the small specimen size may be an obstacle to successful testing.

Importance of Molecular Diagnosis in the Absence of Treatment

An accurate diagnosis is essential even when curative interventions are not available³⁴. In the absence of a definitive treatment, determination of the optimal supportive care is as important and may be determined by the molecular test result. The term supportive at times presupposes that the only

purpose of medical care is to cure or significantly alter the natural progression of a condition through medical interventions such as drugs or surgery. If the interventions cannot cure or alter the progression of a disorder, the implication is that the interventions needed are not medically necessary, do not carry the same level of importance, and perhaps are not properly considered part of medical care. Positive patient outcomes in medicine have not historically been narrowly defined as only cure or prevention of disease. Many diseases are chronic conditions that can be effectively and appropriately managed when curative pharmacological therapies are not available. Healthcare resources are then focused on managing the disorder, the associated comorbidities, effects on other medical conditions, impact on life expectancy and quality of life.

PROGNOSIS

Beyond making a diagnosis, molecular diagnostic testing can provide individualized prognostic information, *i.e.*, the expected clinical outcome in the absence of treatment or with the application of the standard treatment. For inherited disorders, a prognostic marker assesses the likelihood of development of a disease. For oncology, a prognostic marker assesses the prospect of disease progression or survival without disease specific intervention, in contrast to general supportive care. Two key questions to be addressed are (1) does a specific molecular finding have sufficient prognostic evidence to effect a change in management that will improve the clinical outcome, and (2) will the prognosis contribute to personal life management decisions for the patient and the patient's family.

Prognostic Molecular Diagnostics in Inherited Diseases

Many inherited disorders with a similar primary phenotype can later develop distinct associated secondary conditions: for example, hearing loss may be isolated or may be associated with a syndrome. Definitive diagnosis using molecular diagnostic testing can assist with monitoring and/or preparation for these secondary conditions. Usher syndrome patients present with hearing loss but develop retinitis

pigmentosa (night blindness and tunnel vision) as they age (GeneReviews®, <http://www.ncbi.nlm.nih.gov/books/NBK1265/>, accessed 5/6/2015). The presentation of neurofibromatosis is variable and those with a questionable diagnosis based on clinical criteria should receive a definitive diagnosis by molecular diagnostic testing. Patients with neurofibromatosis may develop plexiform neurofibromas that can obstruct or become entangled around vital organs³⁵. Surveillance is critical for these patients; early detection of these tumors will facilitate surgical removal before they become life threatening.

Prognostic Molecular Diagnostics in Oncology

Molecular genetic testing can inform prognosis at the time of diagnosis and guide surveillance and intervention. The presence or absence of a *FLT3-ITD* mutation in cytogenetically normal acute myeloid leukemia has prognostic impact and affects the selection of appropriate treatment even though at present it does not point to specific targeted therapy except in clinical trials³⁶. Molecular testing to quantify mRNA expression of the *BCR-ABL1* fusion gene in CML is an example of using molecular diagnostics to monitor response to therapy, monitor minimal residual disease (surveillance) and in some cases indicate specific changes in therapy³⁷.

Complex prognostic molecular diagnostic tests measuring gene expression have been shown to have clinical utility in treatment of early stage breast cancer. Within the hormone-receptor-positive (ESR1/PGR-positive, or ER/PR-positive) group, demonstrated by immunohistochemistry, chemotherapy is available for those considered at a high risk of recurrence while sparing others considered low-risk the possible complication of chemotherapy-related second malignancies (leukemia/lymphoma). This treatment stratification currently involves the use of genomic/transcriptomic data obtained from the Oncotype Dx™, MammaPrint™, PAM50 and other molecular diagnostic assays. Here the meaning of

prognosis and prediction overlap since the result of the molecular diagnostic can favor chemotherapy (predictive) or favor withholding therapy, a reflection of a good prognosis.

For breast cancers which express neither estrogen and progesterone receptors [ESR1 (ER); PGR (PR)] nor ERBB2 (HER2) (so-called triple negative tumors) the treating physician must consider molecular testing for inherited *BRCA* mutations, potentially facilitating complete care of the patient as well as the extended family. *BRCA* mutation-positive patients may elect to have a prophylactic mastectomy of the uninvolved breast as well as bilateral oophorectomy (GeneReviews®, <http://www.ncbi.nlm.nih.gov/books/NBK1247/>, accessed 6/5/2015)^{38,39}. Similarly, prognostic molecular diagnostics for colon cancer have demonstrated clinical utility in predicting the risk of relapse of stage II colorectal cancers, independent of conventional tumor stage and DNA mismatch repair status^{40,41}.

PRESYMPTOMATIC AND PREDICTIVE TESTING

Molecular diagnostic testing has clinical utility in the context of predictive testing, including evaluation of individuals at high risk of developing a disease due to their family history, predisposition testing in asymptomatic individuals and groups (screening), and risk assessment for multifactorial disorders. Predisposition testing assesses the likelihood that an individual will develop the condition.

Presymptomatic Molecular Testing for Inherited Disease

The clinical utility of utilizing molecular diagnostic testing for inherited disease in asymptomatic individuals depends upon both the condition and whether the test is being performed on a person with a family history or testing within the general population. If the condition has high penetrance, such as Huntington disease, the molecular diagnostic test is used to predict future disease (presymptomatic testing) with high confidence (GeneReviews®, <http://www.ncbi.nlm.nih.gov/books/NBK1305/>, accessed 6/5/2015). Additional types of presymptomatic testing include fetal testing, prenatal screening, newborn screening, or preimplantation genetic diagnosis when a familial mutation is known. In addition to the

assessment of individuals at risk of an inherited disorder is the use of molecular testing to predict drug response due to germline variants in drug metabolizing enzymes and transporters. Pharmacogenomic testing is used to predict drug efficacy, adjust dose, and identify the potential for drug-related adverse events⁴² (PharmGKB®, <https://www.pharmgkb.org/view/dosing-guidelines.do?source=CPIC>, accessed 9/25/2015).

Evaluating the clinical utility of molecular diagnostics used for risk assessment poses an additional challenge in showing that the information from the test result is used to reduce the patient's risk, such as a behavioral/lifestyle change or increased compliance with medical interventions. Significant value, both in improved outcomes and in saving healthcare resources is achieved when molecular testing identifies patients for whom interventions are known to be effective. Key questions to be considered when evaluating the clinical utility of molecular diagnostics for disease risk are whether the test can identify persons not identified through clinical assessment and whether it can provide a more accurate assessment of risk. The value of the molecular diagnostics can be determined by a comparison of the sensitivity and specificity, PPV and NPV of the existing clinical assessment, and clinical risk assessment tools with and without the molecular diagnostic test results⁴³.

Predictive Molecular Testing in Oncology

A predictive factor in oncology is associated with response or lack of response to a particular therapy. A well-studied example is molecular diagnostic testing for mutations in the *KRAS* and *EGFR* genes to determine if EGFR-targeted therapy is appropriate^{27,44}. Particular mutations in either gene serve as predictive factors for the success of EGFR-targeted therapy. Molecular testing can address clinically useful issues beyond drug response, *e.g.*, whether dosing adjustments are needed, whether treatment should be by a different drug and the risk of adverse events. The clinical utility of molecular diagnostics to identify therapy-resistant disease and to optimize dosing is illustrated with gastrointestinal stromal tumors (GIST):

tumors harboring exon 9 mutations in the *KIT* gene have significantly longer progression-free survival if treated with high dosages of the tyrosine kinase inhibitor (imatinib)⁴⁵. The clinical utility of molecular diagnostics to identify therapy-resistant disease is illustrated by the finding that imatinib resistant CML is often due to the development of resistance mutations in the *BCR-ABL1* fusion gene, especially the c.944C>T (p. T315I) mutation. Identifying the mutation is useful to predict the optimal alternative drug⁴⁶, usually mandating a change to a 3rd generation inhibitor.

IMPORTANCE OF MOLECULAR TESTING TO THE HEALTHCARE SYSTEM

Despite the modest cost of a test, an accurate molecular diagnosis can lead to more efficient and appropriate use of health care resources. Most notably, it can stop the repeated office visits and testing associated with the search for a diagnosis in a patient with an unclear clinical situation, which can be very costly. For example, hereditary hemorrhagic telangiectasia is characterized by recurring nosebleeds which have an average age of onset of 12 years. Cerebral and pulmonary arteriovenous malformations (AVM) are typically present but undetected at birth, eventually presenting catastrophically. Such AVM are detectable and treatable if a timely genetic diagnosis is made. Without a molecular assessment, a currently healthy individual with an affected relative is at risk and requires the same monitoring as an affected individual with a proven diagnosis⁴⁷. Evaluation by a specialist is recommended every 5 years for affected or at-risk individuals and includes brain MRI and echocardiogram, with about 20% needing follow-up chest CTs. With an accurate molecular diagnosis unaffected family members will be spared costly procedures and radiation exposure.

Evaluating the impact of molecular diagnosis on the healthcare system in the treatment of cancer is difficult by comparison to inherited disease in which a diagnosis is a discrete endpoint. Although the cost of molecular diagnostic testing is seemingly high, it is negligible compared to the cost of many components of cancer care. Significant expenses arise from molecular diagnostic test results which lead

to the use of targeted or precision therapies. The cost of such therapy is typically two to three orders of magnitude greater than the cost of molecular diagnostic testing. The clinical validity of many mutation–targeted drug associations is well established, especially with respect to dramatic short-term responses in individual cases. It is important to show that precision therapy based on molecular diagnostics leads to improved outcomes. To date this has required large multi-year studies typically assessing one target and one drug. Paradigmatic examples include the use of Gleevec for CML and EGFR inhibitors for lung and colon cancer. The application of MPS panels or exomes and the development of new clinical trial models promise to make this a more efficient process in which one test can assess suitability for many therapies. In patients who have failed traditional therapy, the finding of an actionable mutation on an NGS panel has been associated, in some cases, with dramatic responses^{48–54}. The merit of such off-label use is evaluated at present on a case-by-case basis.

RECOMMENDATIONS

Alternatives to Randomized Controlled Trials

The randomized controlled trial (RCT) remains the gold standard to evaluate interventions but at a practical level not every question of clinical utility can be answered by an RCT. This is especially true for rare inherited diseases and for malignancies, common or rare, driven by uncommon combinations of mutations. The difficulty of obtaining an adequate patient cohort drives up the cost of an adequately powered trial and the accrual of potential benefits to only a small number of patients discourages funding from private or public sources.

Limiting medical care to what has been validated by RCTs is neither practical nor appropriate. Some situations do not require an RCT because observational data and historical controls may be sufficient to define safe practices where pathophysiological knowledge can support an intervention. This is the case with the use of prophylactic thyroidectomy for persons with pathogenic *RET* mutations because family studies have demonstrated previously a high penetrance for these mutations⁵⁵. Additionally, a

recent review indicates that requiring RCTs in conjunction with current evidence-based medicine classification of data quality to assess diagnostic criteria is inadequate, proposing that alternative scales are needed to determine the value of pathology results outside of the limited scope of evaluating RCT drug trial outcomes for prognostic and predictive data⁵⁶.

The RCT is meaningful in some contexts; such as, determining if selecting cancer therapy based on molecular test results improves responses. However, a retrospective study is more suitable for determining if mutations in a particular gene are correlated with a specific clinical presentation. Given these limitations, alternate types of well-designed prospective and retrospective clinical study designs (*e.g.*, case control and other observational studies) and data analysis methods (*e.g.*, comparative effectiveness and decision analysis) should be recognized by stakeholders as appropriate and sufficient for determining clinical utility for molecular diagnostics (Supplemental Figure 3). Recommendations are described in this report, when taken together, describe a new approach to identifying and assessing evidence necessary to demonstrate clinical utility (Supplemental Tables 2 & 3).

Modification of ACCE Framework Application to Molecular Diagnostics

Viewed in the general framework of Alytic validity, Clinical validity, Clinical utility, and Ethical, legal and social implications (ACCE; Centers for Disease Control, <http://www.cdc.gov/genomics/gtesting/ACCE/index.htm>, accessed 6/8/2015), the purpose of molecular diagnostics is to provide critical information to the physician, patient and patient's family which can be used to reduce morbidity and mortality, or to assist the patient or family members with reproductive decision-making. Like the AHRQ guide, ACCE links the utility of the testing with the care provided, using as an example newborn screening tests. If the purpose of a test is to reduce the morbidity or mortality of rare inborn errors of metabolism, that purpose is not achieved unless the child who tests positive is provided with the appropriate intervention and follow-up care. This model can include additional testing,

pre- and post-test counseling, facilities to carry out the testing, and interventions for those who are positive. Our position is that the value of molecular diagnostics are not fully captured by the existing ACCE framework. We therefore propose extensions of the ACCE model and make additional recommendations to incorporate better the value of molecular diagnostic testing into discussions regarding clinical utility (Tables 2 and 3).

Recommendations for a New Approach

The working definition of clinical utility is often narrowed to “actionability,” meaning that molecular diagnostics with established clinical validity must also mandate or inform therapy selection with an expected improvement in health outcome. This attempts to force all molecular diagnostics into a companion diagnostics model for evaluating their clinical utility⁵⁷. This restricted definition excludes a wide range of purposes for molecular diagnostics and ignores many aspects of the clinical utility of a test for the clinician, patient, family, or society (Supplemental Figures 1 & 2). Molecular diagnostic testing results are an intermediate outcome, relying on necessary changes in physician and/or patient behavior to directly link the test results to the typically analyzed health outcomes, such as overall and disease-free survival.

A new approach to evaluate clinical utility in molecular pathology testing procedures is required; traditional models are too constrained or impractical. The existence of evidence for clinical utility that is outside of the norm of traditional models is very different from evidence against clinical utility. Emerging clinical utility evidence published in highly-regarded journals, particularly in emerging technologies, should not be a barrier to insurance coverage and patient access to testing. In summary, we recommend:

- Promotion of patient-centered definitions of clinical utility;

- Utilization of a modified ACCE model incorporating aspects of clinical utility beyond drug selection;
- Support for multiple modalities of clinical utility evidence generation;
- Development of professional organization-driven practice guidelines; and
- Recognition of the critical role of the molecular professional in patient care.

Our complete recommendations (Table 3) and the framework presented here, based on an expanded ACCE model that includes broader parameters for its assessment, recognize the many applications of molecular diagnostic testing and the varied impacts on patients, families and society. In doing so, the capabilities and benefits of molecular diagnostics can be realized while ensuring appropriate access and improved patient outcomes

CONCLUSION

The capabilities and applications of molecular diagnostic testing are rapidly evolving. While alone, individual inherited genetic diseases may be rare, combined they are common. An estimated 2-3% of births have a genetically determined abnormality. By age 25, 5.5% of the population has a medical condition with a significant genetic component. This increases to 60% later in life (Genetic Alliance UK, <http://www.geneticalliance.org.uk/education3.htm>, accessed 6/5/2105), which result in more than half a million deaths per year (Centers for Disease Control, <http://www.cdc.gov/nchs/fastats/leading-causes-of-death.htm>, acceded 6/5/2015). Regardless of the disease, disorder, or condition – even in the absence of a curative therapy – an accurate diagnosis inherently has clinical utility. Molecular pathology testing procedures provides powerful tools for insight and analysis into various aspects of clinical practice, but to reach the goal of providing precision medicine to every patient, the value of elucidating their individual genetic/molecular diagnosis is fundamental to achieving positive downstream patient care outcomes. Without the foundation of an accurate molecular diagnosis, the treating clinician may have to make decisions based on incomplete or inaccurate information. While this practice was often

unavoidable in the pre-genomic medicine era, the post-genomic era enables a higher level of diagnostic precision.

The clinical utility of molecular diagnostics is not limited to diagnosis alone. It also applies to prognosis and prediction. As the clinical utility of an individual molecular diagnostic test is often context dependent, specifying the spectrum of clinical utility that can be addressed by the test is essential. The ability of molecular markers to prospectively identify individuals at risk of disease development, evaluate risk of disease recurrence, or assess the prospect of disease progression/survival provides clinically valuable information utilized by the medical team, patients and their families to provide proactive patient-centered care. This in turn holds societal benefits by focusing medical resources appropriately. As the clinical genomic knowledge base further expands, molecular professionals and the test results they provide and interpret will increasingly be able to classify a patient's disease or disorder and/or guide management. This is the promise of precision medicine.

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Table 1: Definitions and Considerations

Term	Definition	Considerations
Molecular pathology testing procedures (molecular diagnostic)	Any clinical laboratory testing performed to find alterations in nucleic acids in the germline (inherited disease) or in somatic tissues (cancer).	Other applications of molecular diagnostics, such as to infectious disease or HLA typing, are beyond the scope of this document.
Clinical Validity	Ability of a test to correctly classify a patient with respect to a diagnostic, prognostic or predictive category. For example, demonstrating that the results of a test method for identifying microsatellite instability (MSI) in colon cancer correlates with Lynch syndrome, or that the presence of pathogenic mutations in a specific gene are strongly associated with the presence of developmental delay.	The clinical validity for a test, even with respect to a particular application, is not a fixed value. The prevalence of the condition of interest in the population tested affects the positive predictive value (PPV) and negative predictive value (NPV). The significance of a positive result in a patient with a high-risk history will be different from that for a positive result obtained from testing (screening) unselected populations. When a genetic variant affects more than one clinical outcome, the clinical end-point studied needs to be specified. The clinical validity may be high for one endpoint and low for another.
Clinical Utility	Improved patient management is determined based on the results of the test in question compared to management based on results of a different test or no test at all. It includes a wide range of diagnostic, prognostic and predictive applications. The test result is necessary for the care of the patient or a family member, who could be either a future or as yet undiagnosed patient and thus is essential information for the health care professional, the patient, the patient's family, and society.	The clinical utility of molecular diagnostic testing is context dependent. A test can show excellent clinical validity but no clinical utility, depending on the context. Patient outcomes measurements are insufficient because they are greatly impacted by clinical decisions which occur downstream from the molecular diagnostic test result. For clinical utility to be accurately assessed, test results must be correctly interpreted and acted upon. For example, one way to demonstrate the clinical utility of microinstability (MSI) testing would be to show that a specific change in the standard treatment regimen led to better survival for patients with MSI positive tumors than for patients with MSI negative tumors. A different endpoint may show that testing of a proband with an inherited mutation in the MSI pathway led to identification of relatives who are carriers of the mutation and that the identified carriers fared better than did unscreened relatives. An accurate diagnosis has inherent clinical utility and is foundational to directing patient care to improve clinical outcomes.
Cost effectiveness	Impact of a medical test or treatment on the cost of care and/or on patient welfare. The latter is often measured in Quality Adjusted Life Years (QALY).	Although numerous methods have been proposed for quantifying quality of life, or even the cost of treatment, this information is difficult to reliably estimate. Cost-effectiveness analysis (CEA) is not a prerequisite for determining clinical utility, although it often supports evidence for clinical utility when such numbers are available. This type of analysis, although important, is beyond the scope of the present document.

Table 2: Limitations, Concerns, and Suggested Modifications to the ACCE Model List of Targeted Questions Aimed at a Comprehensive Review of Genetic Testing Clinical Utility (Centers for Disease Control, http://www.cdc.gov/genomics/gtesting/ACCE/acce_proj.htm, accessed 6/4/2015)

Component	Targeted Questions	Limitations / Concerns	Suggested Expansion of ACCE Model
Intervention	What is the natural history of the disorder?	Knowledge of underlying genetic variant(s) impact on the natural history of many disorders is still evolving.	Recognize limitations of understanding underlying genetic component impacts on a disorder's natural history, which introduces challenges when defining the clinical utility of molecular diagnostic testing. Remove "Intervention" as the component.
Intervention	What is the impact of a positive (or negative) test on patient care?	Molecular diagnostic test utilization within the oncology and inherited diseases categories can be diagnostic, prognostic, and/or predictive. Each of these can be useful to different stakeholders: clinician, patient, family, society, regulators, and payors.	Define molecular diagnostic test setting and purpose broadly. Include clinical utility purpose to achieve a balance of outcomes where the expected health benefits exceed the expected negative consequences of testing for the person tested.
Intervention	If applicable, are diagnostic tests available?	Interventions are currently narrowly defined as actionability. Many molecular diagnostics will be used for multiple purposes, e.g. to guide treatment and impact morbidity of the genetic condition and to provide information that will influence overall management.	Recognize all therapeutic options are interventions, even when they are not curative. Recognize clinical utility evaluation for molecular diagnostics should be appropriate for the different purposes, in different populations and for the symptoms and presentation being assessed. Define monitoring and patient management as an appropriate intervention.
Intervention Effectiveness	Is there an effective remedy, acceptable action, or other measurable benefit?	Definition of effectiveness often limited to selection of a therapeutic drug (e.g. companion diagnostics model) which is not appropriately applied to all types of molecular diagnostic tests.	Define effectiveness as the ability of the molecular diagnostic test and any associated services to bring out the intended purpose (often, but not invariably, improvements in health) when used under the most favorable circumstances (efficacy) and under routine conditions (effectiveness). Recognize clinician utility: diagnostic, therapeutic, prognostic, and predictive management (even in absence of therapy). Recognize patient utility: disease management, decision-making, family planning, pregnancy management, long-term care decisions. Recognize family utility: impact of molecular diagnostic on family members (presymptomatic or predisposition testing), educational access to caregivers/supportive care. Recognize societal utility: cost of testing and missed diagnosis, economic measures, and healthcare resource management. Change component from "Intervention" to "Effectiveness"
Quality Assurance	What quality assurance measures are in place?	Uncertain many potential reviewers have adequate knowledge base to evaluate the quality of complex molecular diagnostic testing.	Recognize that molecular diagnostic testing is regulated by CLIA & subject to proficiency testing and other QA measures as are other clinical laboratory tests with established clinical utility. Support a modernization of CLIA to better incorporate molecular diagnostic testing.

Pilot Trials Evidence	What are the results of pilot trials?	Pilot trials aren't viewed as being foundational or adequate for reimbursement; RCTs will not exist for many disorders.	Recognize alternates to RCT as appropriate for establishing clinical utility evidence. Change component from "Pilot Trials" to "Evidence"
	What are the financial costs associated with testing? What are the economic benefits associated with actions resulting from testing?	Inadequate data available comparing cost of appropriate molecular diagnostic tests to costs of diagnostic odyssey, unnecessary care, missed diagnosis, healthcare & education systems.	Recognize molecular diagnostic tests can be affordable alternative to costs of diagnostic odyssey, inappropriate / unnecessary utilization of healthcare & educational systems. Identify gaps in appropriate economic outcomes data.
Facilities	What facilities / personnel are available or easily put in place?	Molecular diagnostic testing is widely available but challenges in coverage and payment for professional services remain.	Recognize gaps in coding, coverage and reimbursement for both molecular diagnostic testing and associated professional medical services.
Education	What educational materials have been developed and validated and which of these are available?	Treating physicians often lack information necessary to choose the appropriate test, particularly those in specialties other than those who have utilized molecular testing for years.	Encourage and facilitate collaborative education among relevant professional societies.
	Are there informed consent requirements?	Informed consent does not determine clinical utility of molecular diagnostic test.	Apply informed consent requirements in small number of inherited conditions where it is appropriately utilized.
	What guidelines have been developed for evaluating program performance?	Guidelines for evaluating test analytical & clinical validity are available but guidelines for clinical utility have not reached consensus. Clinical practice guidelines are available for some conditions, but are not available for all disorders/test uses; no systematic reasoning for guideline topic selection; onerous and limits patient access to testing; guidelines don't keep pace with the evidence base.	Do not limit evaluation of clinical utility (and subsequent lack of reimbursement) to rely on the existence of clinical practice guidelines, as this will result in decreased test availability for patients and negative impacts on patient care. Recognize that many disorders will not have clinical practice guidelines available.

Table 3: Recommendations

<p>The following recommendations are made to clinicians, professional organizations and other stakeholders (to include but not limited to federal and state agencies, insurers, managed care organizations, patient advocacy groups, and others involved in health care policy development):</p>
<p>PROMOTE PATIENT-CENTERED DEFINITIONS OF CLINICAL UTILITY</p> <ul style="list-style-type: none"> • Ultimate arbiter of clinical utility is the patient. • Insurer-driven definitions of clinical utility do not necessarily incorporate patient-centered outcome measures such as ethical, legal, and social implications, quality of life improvements, functional status, and patient satisfaction. • Recognize the essential role of an accurate diagnosis in providing patient-centered care. • Recognize the patient's right to be involved in all aspects of their health care and to make fully informed decisions. • Current clinical utility determination models in genetic testing have limitations and harms: <ul style="list-style-type: none"> ○ A laboratory test result in isolation is only a portion of the entire professional medical service and needs to be viewed in that context. Meaningful use of a test (the indication for testing and interpretation of that test in the context of the individual patient's management) will impact a test's clinical utility. ○ Defining clinical outcomes depends upon a specific disease being diagnosed and/or managed using molecular methods. ○ There are identifiable patient harms to limiting access to genetic testing based upon an unrealistic evidentiary level for clinical utility. Insufficient evidence for lack of clinical utility evidence, particularly in emerging technologies, should not be a barrier to reimbursement and patient access to testing. A lack of evidence for clinical utility is not the same as evidence for a lack of clinical utility.
<p>PROPOSE UTILIZING A MODIFIED ACCE MODEL THAT INCORPORATES THE ASPECTS OF CLINICAL UTILITY BEYOND DRUG SELECTION</p> <ul style="list-style-type: none"> • Recognize that an accurate molecular diagnosis has inherent clinical utility. • Establish that predictive and prognostic molecular diagnostic testing can also demonstrate clinical utility when evaluated in context. • Describe three purposes for tests: to reduce morbidity or mortality, to provide information salient to the care of the patient or family members, and/or to assist the patient or family members with reproductive decision-making. • Do not restrict the definition of clinical utility to selection of a pharmacological intervention. • See Table 2 for suggested modifications to the list of targeted questions aimed at clinical utility.
<p>SUPPORT MULTIPLE MODALITIES FOR ESTABLISHING EVIDENCE TO EVALUATE CLINICAL UTILITY</p> <ul style="list-style-type: none"> • Support the development of clinical grade high-quality databases of outcomes together with the related and genetic information for oncology and inherited disease. • Support retrospective data evaluation from n-of-one trials and compassionate use/off-label use exception uses of approved therapies. • Support alternative clinical trial modalities such as bucket and basket trial designs in oncology with molecular marker identification and/or molecular diagnosis driven selection of treatment arms. • Development of a national database of anecdotal and small case series that involve n-of-one correlations of response to treatment information correlated with genetic information in oncology. This information can be used to develop better RCT to answer pressing questions in interpretation of molecular diagnostic testing, and help in decision making in the absence of sufficient RCT data. • National database development for rare diseases correlated with genetic information in inherited diseases. As more patients with inherited disorders are correctly classified, we will learn a great deal about the knowledge of the disorders, and their natural histories and genotype phenotype correlations, which will then be useful in the interpretation of genetic data, will be greatly extended, and, in some cases, open avenues for new therapies, especially now that several new methods for editing the genome have been developed.
<p>SUPPORT THE DEVELOPMENT OF PROFESSIONAL ORGANIZATION-DRIVEN PRACTICE GUIDELINES</p> <ul style="list-style-type: none"> • Professional organization-driven guidelines should be used as part of the chain of evidence to develop clinical utility. • Encourage efforts to develop collaborative interdisciplinary clinical practice guidelines. • Support professional organization-driven development of peer-to-peer clinical laboratory practice guidelines to guide best practices, particularly in areas of new/emerging technologies, and to assist clinicians in and stakeholder evaluation of molecular diagnostics and interpretation of results. • Support professional organization-driven development of interim clinical practice guidelines and expert opinion guidance documents that address aspects of clinical utility where RCT evidence is minimal and/or emergent technologies are utilized. • Support development of appropriate evidence-based medicine tools for evaluation of molecular diagnostics and pathology literature. • Increase engagement between professional associations and other stakeholders, such as FDA, CMS, payers, community service providers, and patient groups. • Encourage incorporation of comparative effectiveness research and health economics consideration into professional practice guidelines. • Increase available AHRQ / CDC / IOM / PCORI grant funding to support these projects.
<p>RECOGNIZE THE CRITICAL ROLE OF THE MOLECULAR PROFESSIONAL IN DISEASE MANAGEMENT</p> <ul style="list-style-type: none"> • Molecular pathologists and clinical molecular geneticists are key medical professionals with specialized knowledge needed to guide patient management decisions.

- Molecular diagnostics professionals have the education, training, and board certifications to appropriately guide test selection and utilization and should be relied upon by treating clinicians.
- Patient's team of medical providers – molecular pathologists, medical geneticists, pathologists, oncologists, genetic counselors, surgeons, primary care providers, other providers – all have distinct scopes of practice that work in concert to support disease management and improve outcomes.
- Professional teams already have existing quality metrics and oversight mechanisms to guide proper test utilization (laboratory accreditation, practice guidelines, standards of care, tumor boards, medical staff reviews).

AHRQ – Agency for Healthcare Research and Quality; CDC – Centers for Disease Control; IOM – Institute of Medicine; PCORI – Patient-Centered Outcomes Research Institute; FDA – Food & Drug Administration; CMS – Centers for Medicare & Medicaid Services